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Water insoluble polymers as efficient binder in fluid bed granulation of metoprolol for preparation hydrophilic matrix extended-release tablets

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Abstract

Objectives. *The objective of this study was to investigate the possibility of developing metoprolol extended-release tablets by using hydroxypropyl methylcellulose (HPMC) in order to obtain the hydrophilic matrix and Eudragit NE 40D, Kollicoat SR 30D and Surelease E7 as binders during the granulation process.*

Material and methods. *The extended-release tablets were prepared via fluid bed granulation of metoprolol powder using Eudragit NE 40D / Kollicoat SR 30D / Surelease E7 as binders, followed by compression. The influence of three formulation factors (the type of granulation polymers, the ratio of granulation polymers and the HPMC ratio) on the kinetic metoprolol tartrate release was investigated through a full factorial experimental design.*

Outcomes. *The kinetic release of all 26 formulations was best fitted with Peppas model. According to n values of Peppas equation, the release mechanism of drug consists in water diffusion into the matrix, followed by matrix swelling and erosion. The results also indicated that the formulations containing an increased amount of Eudragit NE (10% or more) as binder in the granulation process presented a satisfactory release rate of metoprolol over 12 hours from the granules incorporated in the hydrophilic matrix.*

Conclusions. *This study demonstrated the possibility of lowering of the burst effect from hydrophilic matrix extended-release dosage forms incorporating a freely soluble drug, by granulating the drug with a high amount of Eudragit NE 40D and processing the obtained granules in a hydrophilic matrix by tableting.*

Keywords: metoprolol, hydrophilic matrix, extended-release, Eudragit NE, Kollicoat, Surelease, HPMC

INTRODUCTION

The extended-release oral drug delivery systems are characterized by their ability to drug release continuously, over an extended period of 12-24 h, offering several advantages, such as improved dosage regimens, increased compliance, a better therapeutic effect and lower side-effects [1,2]. The most common type of extended-release oral dosage forms is the hydrophilic matrix, which is usually obtained from cellulose ethers such as hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC) [3,4]. Hydroxypropyl

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methylcellulose (HPMC) is a semisynthetic polymer available in several grades that vary according to degree and ratio of substitution of the hydroxypropyl and methoxyl groups and therefore in hydration rate and water viscosity; it is widely used in pharmaceutical as matrix-forming polymer in preparation of extended-release oral tablets [4]. Even when high-viscosity grades of HPMC are used, obtaining hydrophilic matrix extended-release oral dosage forms with metoprolol (a freely wate- soluble drugs) is difficult due to initial high amount release [5]. The aqueous dispersions of water insoluble coating polymers as ethylcellulose (e.g. Aquacoat ECD, Surelease), methacrylic derivatives (e.g. Eudragit NE 40D) or polyvinyl acetate (e.g. Kollicoat SR 30D), create an insoluble but permeable film and are commonly used to coat pellets, granules, or tablets in order to obtain reservoir-type modified release oral dosage form [6-9].

Generally an initial burst effect can be observed when incorporating freely water-soluble drugs into the hydrophilic matrices. Therefore, adding water-insoluble coating polymers as binders during the fluid bed granulation process of freely water-soluble drug in association with high-viscosity HPMC as matrix-forming polymer could solve this problem by partially coating the freely water-soluble drug and thus reducing the penetration of water in the matrix, slowing the drug solubilization which will consequently determine a decreased of the initial drug diffusion with the reduction of the burst effect. The water-insoluble coating polymers that could be used as binders in fluid bed granulation of freely water-soluble drugs include, among others, polyvinyl acetate (Kollicoat SR) ethylcellulose (Surelease), and methacrylic acid copolymers (Eudragit NE) [10,11].

Design of experiments (DoE) is a powerful tool which reveals, through systematic approach, the most important formulation factors or process parameters that may affect the product characteristics. By using DoE, it is able to find, in a time and resource efficient manner, the level at which a factor determines the achievement of an optimum product and process [12-14].

The aim of this work was to investigate whether, it is possible, by using aqueous dispersions of insoluble coating polymers, Kollicoat, Eudragit and Surelease, as binders in preparation of granules via fluid bed granulation together with high viscosity HPMC (Methocel K100 M) as matrix-forming polymer in tableting, could reduce the burst effect of metoprolol, a freely water-soluble drug, in hydrophilic matrix extended-release tablets as oral dosage forms.

MATERIAL AND METHODS

Materials

Metoprolol tartrate (from Microsin, Romania) as drug substance; lactose monohydrate 200 mesh (from Meggle, Germany) and microcrystalline cellulose PH102 (from JRS, Germany) as filler in granulation;; hydroxypropyl methylcellulose (HPMC) - Methocel K100 M (from Colorcon, UK) as matrix forming; direct compressible lactose – Tablettose 80M (from Meggle, Germany) as filler in tableting; fumed silica – Aerosil 200 (from Degussa, Germany) and magnesium stearate (from Merck, Germany) as lowing agents; Kollicoat SR 30D (from BASF, Germany); Eudragit NE 40D (from Degussa, Germany); Surelease E7 19010 (from Colorcon, UK) insoluble coating polymers used as binding agents in fluid bed granulation.

Design of experiment (DoE)

A full factorial design of experiment (DoE) with three factors and three levels was used to study the influence of three formulation factors on the pharmaceutical characteristics of the hydrophilic matrix extended-release tablets. Table 1 illustrates the formulation factors and their level of variation, while table 2 shows the design of experiment matrix. Modde software (Sartorius Stedim Data Analytics AB, Sweden) was used to build the experimental design of the study, as well as to calculate the coefficients, statistical parameters and fitting of the experimental data [15].

Granules preparation

The granulation process was conducted in a Strea 1 fluid bed granulator (from Aeromatic A.G., Switzerland). The granulation formula and the processing conditions are presented in table 3. After the binder solution spraying completed, the granules were maintained for another 30 minutes in the fluid bed granulator at 60°C and low fluidization air fan, in order to be properly dry the granules. According with design of experiment matrix, the ratios of the three insoluble polymers used as binders in aqueous dispersions (Kollicoat SR 30D, Eudragit NE 40D and Surelease E7) were 4%, 8% and 12%.

Tablets preparation

The tablets (weight 450 mg, 100 mg metoprolol tartrate/tablet) were prepared using an eccentric

TABLE 1. Formulation factors (independent variables) and their level of variation

Variables	Symbol	Levels		
		-1	0	+1
Type of granulation polymer	X_1	Eudragit	Kollicoat	Surelease
Ratio of granulation polymer (%)	X_2	4	8	12
HPMC ratio (%)	X_3	20	30	40

TABLE 3. Granulation formula and fluid bed granulator processing parameters

Granulation formula	% (m/m
Metoprolol tartrate	27.78 %
Lactose monohydrate	30 %
Binder (Eudragit NE 40D / Kollicoat SR 30D / Surelease E7 19010*	4-8-12 %
Purified water **	q.s.
Fluid bed granulator processing parameters	
Binder solution spray rate – peristaltic pump speed (rpm)	10
Diameter of the gun nozzle (mm)	0.8
Atomization air pressure (atm.)	1
Fan air (m3/min)	3-5
Inlet Air Temperature (0C)	70
Outlet Air Temperature (0C)	27-33
Granulation process duration (min)	25

* according to the design of experiment matrix, see Table II
** needed to prepare a binder solution with 26% polymer content

TABLE 2. Design of experiment (DoE) matrix

Experiment Name	Run Order	X1	X2	X3
Exp 1	2	Eudragit	4	20
Exp 2	18	Eudragit	4	30
Exp 3	26	Eudragit	4	40
Exp 4	14	Eudragit	8	20
Exp 5	9	Eudragit	8	30
Exp 6	20	Eudragit	8	40
Exp 7	7	Eudragit	12	20
Exp 8	29	Eudragit	12	30
Exp 9	13	Eudragit	12	40
Exp 10	21	Eudragit	8	30
Exp 11	17	Kollicoat	4	20
Exp 12	11	Kollicoat	4	30
Exp 13	6	Kollicoat	4	40
Exp 14	25	Kollicoat	8	20
Exp 15	23	Kollicoat	8	30
Exp 16	4	Kollicoat	8	40
Exp 17	22	Surelease	4	20
Exp 18	12	Surelease	4	30
Exp 19	19	Surelease	4	40
Exp 20	3	Surelease	8	20
Exp 21	5	Surelease	8	30
Exp 22	27	Surelease	8	40
Exp 23	1	Surelease	12	20
Exp 24	16	Surelease	12	30
Exp 25	15	Surelease	12	40
Exp 26	24	Surelease	8	30

X1 - granulation polymer type, X2 – Ratio of granulation polymer, X3 – HPMC ratio

tablet press EK0 (from Korsch, Germany), equipped with 10 mm diameter lenticular set of punch and die. The composition of the extended-release tablets included: 50% metoprolol granules, 1% silicon dioxide, 1% magnesium stearate, 20-30-40% HPMC according with the design of experiment matrix, and the difference to 100% being represented by direct compressible lactose.

Determination of the DoE's dependent variables

The responses of the design of experiment (dependent variables) were the Peppas kinetic equation coefficients, k and n and the percents (%) of metoprolol released at different time intervals (1, 2, 3, 4, 6, 8, 12 hours) during a period of 12 hours. The release of metoprolol from the extended-release tablets was evaluated according to the officinal procedure for European Pharmacopoeia ("2.9.3. Dissolution test for solid dosage forms"): The dissolution test was performed using the following dissolution conditions: dissolution tester, apparatus no. 2 (paddle) from PharmaTest, Germany; dissolution medium: 900 mL phosphate buffer at pH 6.8; dissolution temperature: 37°C; agitation: 50 rpm of the paddle; drug assay, using a validated UV – spectrometric method at 275 nm.

Investigation of the release kinetics of the drug

In order to determine the release kinetics of metoprolol from the extended-release tablets, the experimental data were fitted with the following mathematical equations: Korsmeyer-Peppas, Higuchi, zero order, Hixon-Crowell, Baker-Lonsdale, and first order (the equation are presented in table 4). In order to avoid overfitting only a value greater than 80% was considered when calculating the release kinetics [16-18]. Also, the correlation coefficient must be nearly 1 [16,17] and the Akaike index must have the lowest value to consider that the release kinetics is adequate [18].

TABLE 4. Mathematical models of drug release

Higuchi	Qt/Q∞=Kt0.5
Korsmeyer - Peppas	Qt/Q∞=Ktn
Zero Order	Qt=Q0+Kt
Hixson-Crowell	Q01/3−Qt1/3=Kt
Baker-Lonsdale	[3/2][1−[1−[Qt/Q∞]2/3]−[Qt/Q∞]=Kt
First Order	Qt/Q∞=Kt

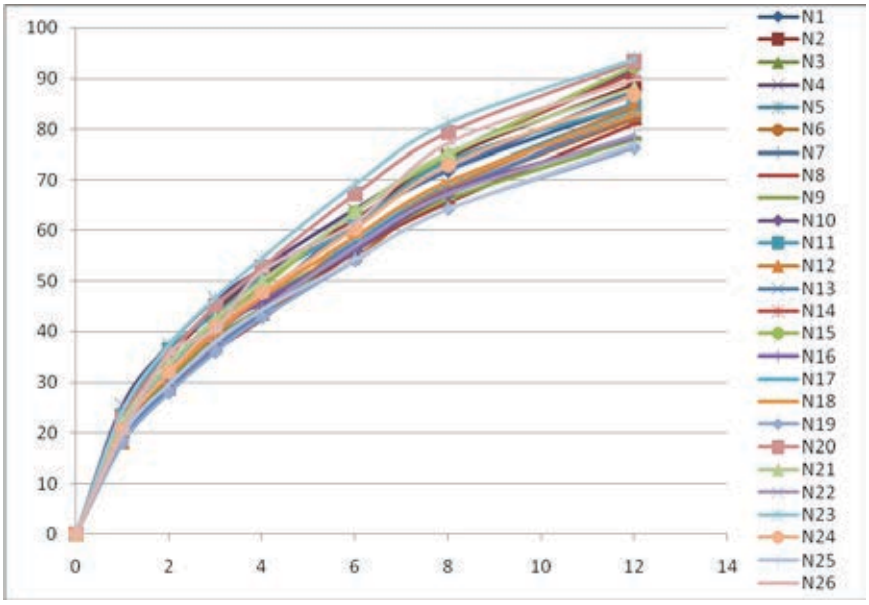


FIGURE 1. Dissolution profiles of metoprolol tartrate at in vitro release from hydrophilic matrix extended-release tablets

RESULTS AND DISCUSSION

The type of polymers (Eudragit NE 40D, Kollicoat SR 30D or Surelease E7) used as binder in granulation, the ratio of granulation polymers and the ratio of HPMC were formulation factors, whose influence on metoprolol release profile and type of kinetics was investigated using a full factorial experimental design. The in vitro release profiles of metoprolol tartrate from all the formulations prepared according to the design of experiment matrix are presented in Fig. 1. The all the pharmaceutical properties of the extended-release tablets (weight uniformity, tablets friability, tablets hardness) of the prepared formulations were within European Pharmacopeia limits.

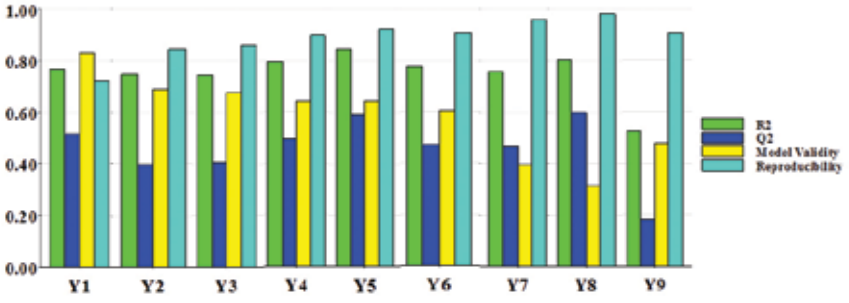
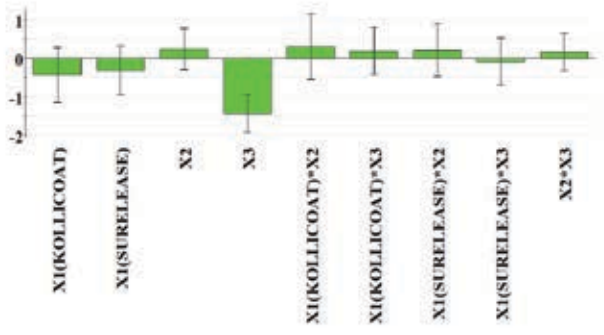


FIGURE 2. Summary of fit of the experiment's design
Y1 – % of metoprolol released after 1 hour, Y2 – % of metoprolol released after 2 hours, Y3 – % of metoprolol released after t 4 hours, Y4 – % of metoprolol released after 4 hours, Y5 – % of metoprolol released after 6 hours, Y6 – % of metoprolol released after 8 hours, Y7 – % of metoprolol released after 12 hours, Y8 – k Peppas, Y9 – n Peppas

Data fitting, coefficients calculation, statistical parameters evaluation and validation of the experimental design were performed using Modde software [19]. The Partial Least Squares [PLS] regression method was used for coefficients calculation and experimental data fitting. The values of R2 and Q2 were used to analyse the validity of the experimental design [9,20].
Fig. 2 illustrates the overall fitting of the experimental data, as well as the statistical parameters R2 și Q2, model validity and reproducibility. The values of R2 were greater than 0.7 for responses Y1-Y8, demonstrating a good fitting, and not a satisfactory fitting for the response Y9 (n Peppas).

Figure 3 presents the influence of the formulation variables on responses as coefficient plot and figure 4 presents the influence of the formulation variables on responses as contour plot surface.

The kinetic release of metoprolol from the prepared extended-release tablets was evaluated by using six mathematical models (Table 4). Table 5 shows the results obtained following fitting the data with different kinetic equations for all the prepared extended-release tablets (N1 – N26).



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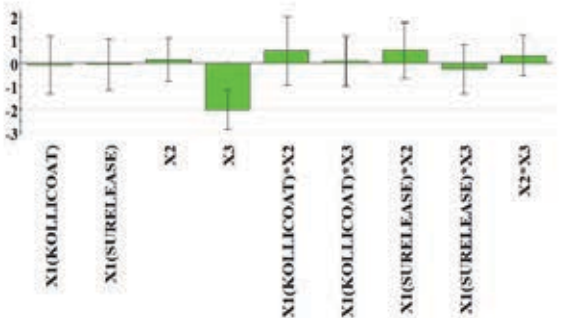

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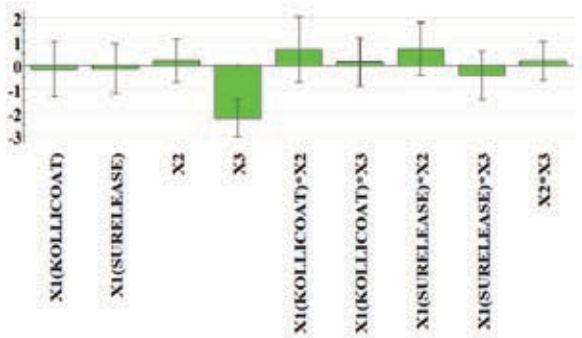

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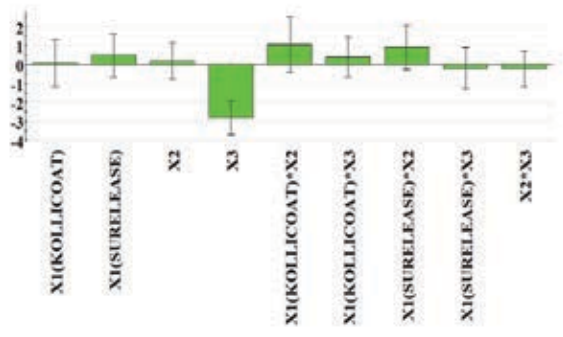

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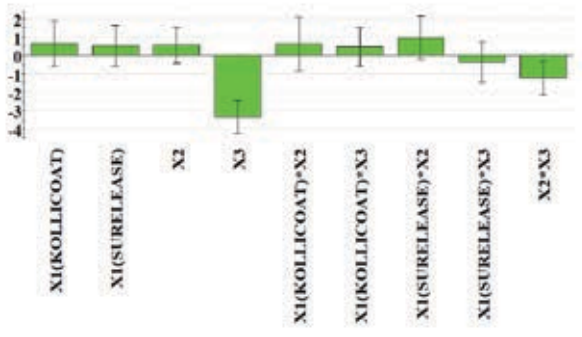

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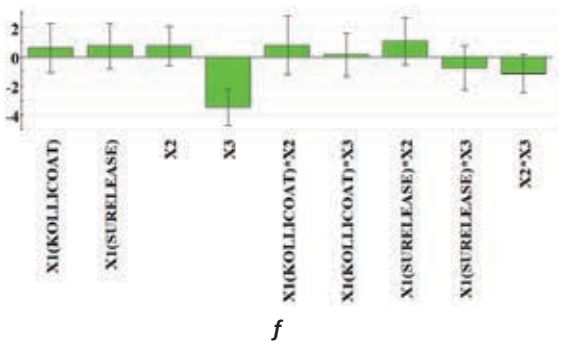

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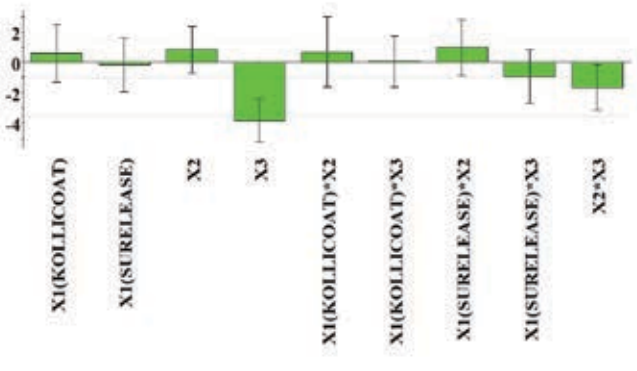

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FIGURE 3. Coefficients' plots presentation illustrating the influence of formulation factors a – % of metoprolol released after 1 hour (Y1), b – % of metoprolol released after 2 hours (Y2), c – % of metoprolol released after 4 hours (Y3), d – % of metoprolol released after 4 hours (Y4), e – % of metoprolol released after 6 hours (Y5), f – % of metoprolol released after 8 hours (Y6), g – % of metoprolol released after 12 hours (Y7). X1 – type of granulation polymer, X2 – ratio of granulation polymer, X3 – HPMC ratio

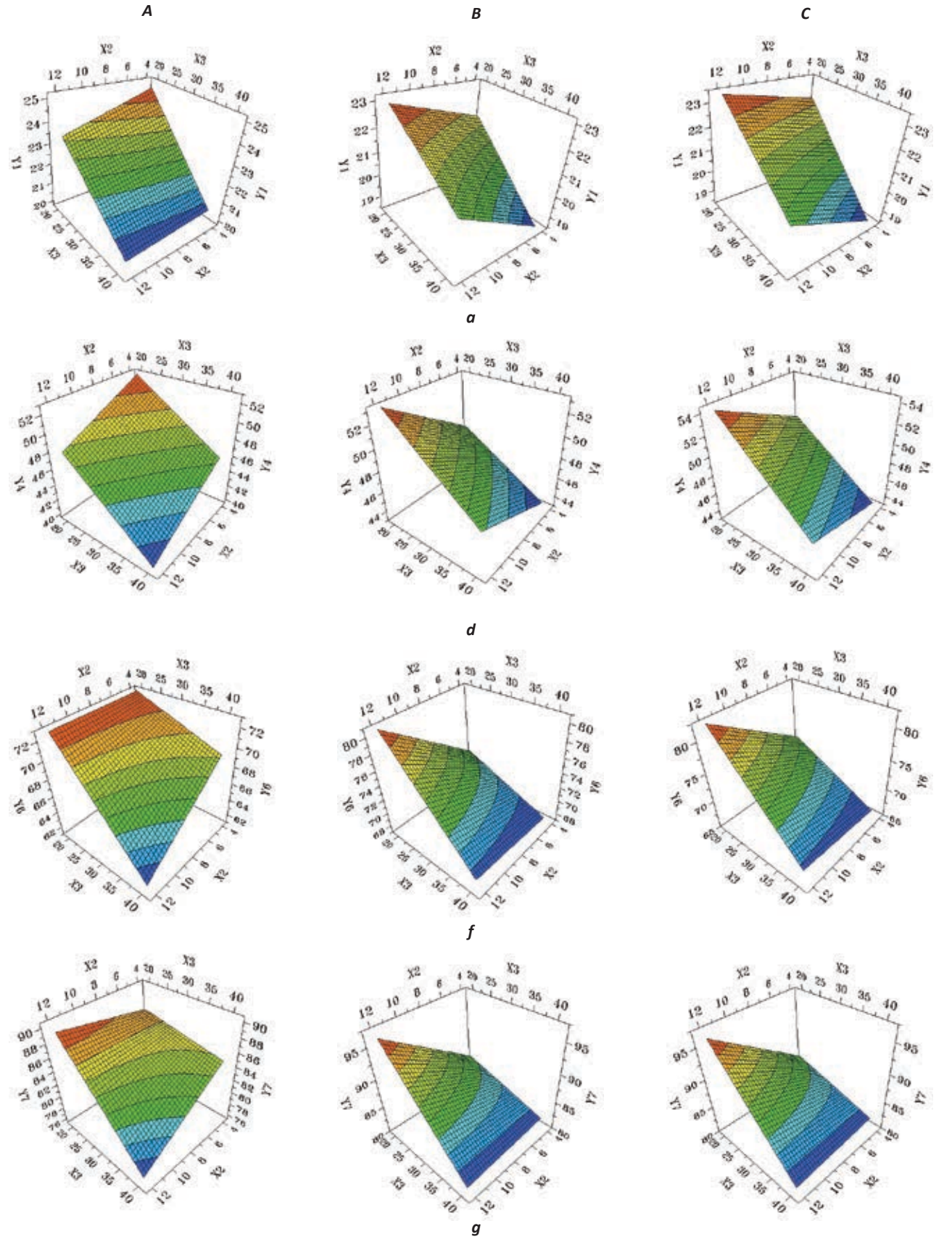

FIGURE 4. Contour plots illustrating the influence of formulation factors on metoprolol release
A – Eudragit; B- Kollicoat; C – Surelease. a – % of metoprolol released after 1 hour (Y1), d – % of metoprolol released after 4 hours (Y4), f – % of metoprolol released after 8 hours (Y6), g – % of metoprolol released after 12 hours (Y7). X1 – type of granulation polymer, X2 – ratio of granulation polymer, X3 – HPMC ratio

TABLE 5. Results from fitting the dissolution profile with different kinetic equations

	Higuchi			Korsmeyer - Peppas				Zero order		
	k	r^2	AIC	K	n	r^2	AIC	k	r^2	AIC
Exp 1	25.10	0.998	14.77	25.73	0.486	0.998	15.50	8.760	0.613	46.49
Exp 2	25.61	0.998	15.83	24.54	0.522	0.999	14.01	8.995	0.728	45.69
Exp 3	23.23	0.994	22.42	20.61	0.563	0.999	3.961	8.217	0.813	43.22
Exp 4	26.42	0.999	5.250	26.15	0.505	0.999	6.14	9.257	0.681	46.46
Exp 5	23.88	0.997	17.71	22.29	0.536	0.999	11.33	8.412	0.762	44.36
Exp 6	22.89	0.992	24.21	20.03	0.570	0.999	14.27	8.103	0.823	42.88
Exp 7	24.75	0.994	23.00	22.25	0.556	0.998	15.46	8.743	0.799	44.25
Exp 8	22.57	0.992	23.95	19.78	0.569	0.998	14.60	7.991	0.821	42.70
Exp 9	22.92	0.998	14.31	22.99	0.498	0.998	16.29	8.015	0.655	45.11
Exp 10	23.51	0.997	17.65	22.12	0.532	0.998	14.41	8.277	0.752	44.29
Exp 11	25.07	0.997	18.65	25.29	0.495	0.997	20.58	8.765	0.644	46.28
Exp 12	23.42	0.987	28.29	19.42	0.598	0.998	16.78	8.325	0.861	42.37
Exp 13	23.09	0.989	31.08	19.56	0.587	0.998	16.73	8.196	0.847	42.56
Exp 14	25.63	0.992	25.77	22.41	0.571	0.998	16.16	9.071	0.823	44.31
Exp 15	25.71	0.991	27.20	21.96	0.583	0.999	13.67	9.121	0.842	43.92
Exp 16	23.04	0.997	17.86	22.55	0.511	0.997	19.42	8.074	0.695	44.85
Exp 17	23.96	0.998	15.24	22.84	0.525	0.999	12.17	8.422	0.735	44.81
Exp 18	23.80	0.996	20.52	22.04	0.540	0.998	17.08	8.381	0.768	44.37
Exp 19	21.78	0.993	22.84	19.56	0.556	0.997	18.44	7.688	0.798	42.89
Exp 20	26.94	0.995	23.55	24.87	0.542	0.997	21.36	9.491	0.770	45.87
Exp 21	25.48	0.995	22.63	23.65	0.539	0.997	20.96	8.972	0.764	45.29
Exp 22	22.70	0.994	22.09	20.86	0.545	0.997	19.83	8.000	0.775	43.75
Exp 23	27.56	0.996	22.17	26.50	0.521	0.996	23.10	9.672	0.720	46.80
Exp 24	24.67	0.993	23.97	22.08	0.559	0.998	17.82	8.716	0.803	44.25
Exp 25	22.18	0.997	15.98	21.05	0.527	0.999	13.59	7.798	0.740	43.8
Exp 26	25.72	0.989	27.58	23.07	0.557	0.994	26.25	9.081	0.797	44.98

	Hixon and Crowell			Baker and Lonsdale			First order		
	k	r^2	AIC	K	r^2	AIC	k	r^2	AIC
Exp 1	0.933	0.949	37.04	0.0156	0.987	27.27	0.178	0.972	31.86
Exp 2	0.961	0.950	34.70	0.0162	0.975	32.01	0.182	0.984	29.43
Exp 3	0.042	0.964	33.68	0.0126	0.969	32.90	0.150	0.984	28.95
Exp 4	0.053	0.952	35.94	0.0176	0.978	31.35	0.194	0.977	31.47
Exp 5	0.044	0.953	35.14	0.0136	0.975	31.52	0.159	0.978	30.65
Exp 6	0.041	0.967	33.21	0.0122	0.967	33.21	0.146	0.985	28.29
Exp 7	0.047	0.971	33.13	0.0148	0.966	34.01	0.169	0.986	28.54
Exp 8	0.040	0.964	33.47	0.0118	0.967	32.89	0.142	0.983	28.92
Exp 9	0.042	0.920	37.24	0.0124	0.988	32.89	0.149	0.963	32.64
Exp 10	0.043	0.946	35.76	0.0131	0.976	30.90	0.154	0.973	31.57
Exp 11	0.049	0.939	36.61	0.0155	0.983	29.01	0.177	0.974	31.53
Exp 12	0.043	0.983	29.93	0.0128	0.957	35.55	0.152	0.994	23.23
Exp 13	0.042	0.979	26.91	0.0124	0.962	34.57	0.148	0.993	24.34
Exp 14	0.050	0.983	30.69	0.0161	0.960	35.77	0.180	0.992	25.79
Exp 15	0.050	0.985	29.95	0.0161	0.956	36.60	0.180	0.992	26.33
Exp 16	0.042	0.934	36.43	0.0125	0.983	28.26	0.150	0.971	31.52
Exp 17	0.045	0.951	35.38	0.0138	0.979	30.40	0.161	0.979	30.21
Exp 18	0.044	0.962	34.15	0.0135	0.974	31.74	0.158	0.986	28.11
Exp 19	0.038	0.957	34.01	0.0108	0.974	31.16	0.135	0.984	28.25
Exp 20	0.055	0.982	31.05	0.0184	0.965	35.17	0.200	0.993	25.40
Exp 21	0.050	0.974	32.74	0.0160	0.970	33.52	0.180	0.991	25.95
Exp 22	0.041	0.957	34.36	0.0120	0.975	31.19	0.146	0.984	28.51
Exp 23	0.058	0.979	32.02	0.0196	0.969	34.22	0.211	0.992	26.02
Exp 24	0.047	0.975	32.32	0.0147	0.966	34.09	0.168	0.991	26.18
Exp 25	0.039	0.939	35.81	0.0114	0.982	28.64	0.140	0.973	31.01
Exp 26	0.051	0.978	32.20	0.0163	0.960	35.63	0.182	0.990	27.31

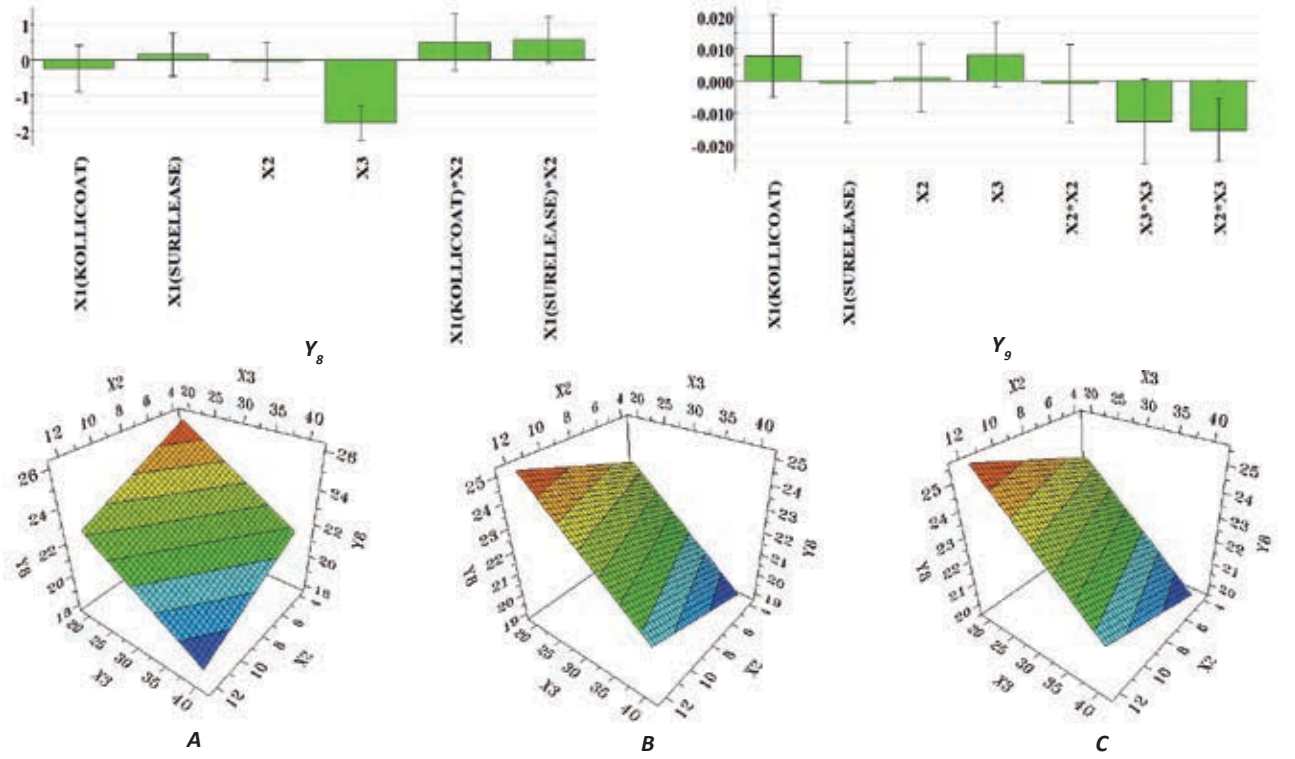

FIGURE 5. Regression of coefficients' plots and contour surface plots showing the influence of the formulation factors on kinetic release parameters
X1 – Granulation polymer type, X2 – ratio of granulation polymer, X3 – HPMC ratio; Y8 – k Peppas, Y9 – n Peppas
A – Eudragit; B - Kollicoat; C – Surelease

The coefficients of the equation used to fit the experimental data with the chosen model for kinetic release evaluation are present in fig. 5 scaled and centred plots (in Fig. 5, Y8 and Y9,) and as response surface plot (in Fig. 5. A, B, C).

Fig. 3 and Fig. 4 illustrate, in the form of coefficient plots and contour plot surfaces, respectively, the effect which the formulation factors and their interaction had on the release of metoprolol from the extended-release tablets. The coefficients analysis revealed that HPMC ratio (X3) is the main factor that affected metoprolol's release, namely an increase in the amount of Methocel K100 M reduced the drug release rate at all dissolution time points (Fig 3. a-g). As respects the influence of the polymer type (X1) used for the granulation process, only Eudragit reduced the dissolution rate of drug released at all time points (Fig 4A), and the influence of Kollicoat and Surelease are dependent on the HPMC ratio and the dissolution time point (Fig. 4B – Kollicoat; Fig. 4C – Surelease). The influence of the binder polymer ratio on metoprolol released was different, depending on the granulation polymer type (X1). A greater amount of Eudragit decreased the percentage of metoprolol released at all dissolution time points (Fig. 4A), while increasing the amount of Kollicoat and Surelease increased the percentage of metoprolol released in the first 6 hours (Fig. 4B – a,d; Fig 4C - a,d) and had no effect after 6 hours if a high amount of HPMC was used (Fig. 4B – e,g; Fig 4C– e,g). The fact that the drug release increased instead of decreasing at higher Kollicoat and Surelease concentrations may be explained by the following: when increasing granulation polymer amount (Kollicoat or Surelease), the polymer layer becomes thicker and its plasticity is reduced. As a result, the polymer's flexibility decreases, its brittleness increases and determines its rupture at the time of compression.

DISCUSSION

According to literature data, ethylcellulose appears to be a more brittle polymer than acrylic polymers, therefore the latter are preferred for coating of multiparticulate systems before their compression, due to their increased flexibility [21]. Similar results were obtained by other researchers, regarding the drug release kinetics profile by different polymers. Nellore et al. examined the metoprolol kinetics release from hydrophilic matrix tablets prepared with different percent of HPMC, ranging from 10% to 40%.

They observed that an increase of the amount of HPMC from 10% to 40 in hydrophilic matrix tablets prepared via direct compression, conduct to a significant reduction of the metoprolol tartrate release rate. However, for hydrophilic matrix tablets prepared trough fluid bed granulation, the influence was less clear [20]. Muschert et al. obtained different results from the ones obtained in the present study, namely they described a reduction of the diltiazem release rate from coated pellets with ethylcellulose [22].

The kinetic release of metoprolol tartrate from the extended-release hydrophilic matrix tablets was evaluated using six mathematical models (presented in Table IV). Table V shows the results and the statistical parameters obtained at kinetics release characterization. All formulations (N1 – N26) fitted best with the Peppas model from the kinetic release profile point of view. Following this finding, k and n parameters of Peppas equation were introduced as responses (Y8 – k and Y9 – n) of the DoE in order to evaluate the effect of the studied formulation factors on the metoprolol kinetic release. Fig. 5 revealed that the HPMC ratio (X3) was the only factor that influenced the parameter k Peppas, namely the value of k Peppas decreased when the HPMC ratio increased. The influence of the ratio of the polymer and the type of polymer used for the granulation process (Eudragit, Kollicoat, and Surelease) were insignificant. The analysis of coefficients did not identify any interactions between the studied formulation factors. The percentage of the drug released was different depending on the granulation polymer type (Fig. 5): increasing the amount of Eudragit reduced k Peppas, while increasing the amount of Kollicoat and Surelease increased k Peppas. The formulation factors had a similar influence on the parameter k Peppas as on the in vitro release of metoprolol tartrate. The results obtained by other researchers were similar with the ones obtained in this study, showing that an enhancement of polymer concentration (Kollidon SR) decreased k Peppas release constant [29]. The studied formulation factors have not influenced on the n Peppas parameter, as no correlation between the formulation factors and n Peppas parameter was identified. All the values of n are close to 0.5 (with low variability between 0.48 and 0.58) that suggest a system with Higuchi kinetic release behaviour.

Based on scientific literature information, matrix tablets with HPMC or other hydrophilic polymers determine a complex drug kinetic release, which includes swelling, diffusion and erosion steps and is based on Korsmeyer-Peppas kinetic release mathematical model [23-29]. Generally, the drug release from hydrophilic matrix tablets takes place in three steps: (1) the infiltration of the dissolution medium into the matrix and its hydration; (2) the swelling and the erosion of the matrix; (3) the transfer of the dissolved drug through the hydrated and swollen matrix, or the transfer of matrix fragments into the dissolution medium [4,29]. However, the results of this study showed that drug release occurs after a Higuchi model (n Peppas model's mechanism for a n value close to 0.5 is similar to Higuchi's model) [30]. Therefore, the extended-release tablets obtained with the two types of polymers (high viscosity HPMC and Eudragit / Kollicoat / Surelease) appear to determine a release which happens after a Higuchi model [25,27,30]. Shoaib et al. obtained similar results, namely observed a release kinetics which happened after a Higuchi model for ibuprofen HPMC matrix tablets [24]. Finally, according to n Peppas, metoprolol exhibited a kinetic release from the prepared tablets which consisted in the diffusion and erosion of the matrix [25,30].

CONCLUSIONS

In this study, hydrophilic HPMC matrix extended-release tablets were developed using design of experiments. Three formulation factors were chosen to be studied - type of granulation polymer, ratio of granulation polymer and HPMC ratio, in order to evaluate their influence on the metoprolol kinetic release. The conclusions that could be drawn from this study are the following: HMPC ratio (X3) was the main factor that affected drug release during the 12 hours dissolution test, as the results showed a reduction of the released drug percentage at all dissolution points following the increase of HPMC ratio; regarding the polymer type and ratio, Eudragit was the only polymer used as binder in fluid bed granulation that determined the decrease of the amount of metoprolol released at all dissolution points, while increasing the ratio of Kollicoat and Surelease determined an increase of the percent of metoprolol released in the first 4 hours, but did not influence the release after 6 hours for formulations with a high amount of HPMC; the kinetic release fitted best with Peppas model for all formulations, and the value of n of Peppas model was close of 0.5, which proves that metoprolol release was determined

by drug diffusion and matrix erosion, according to a Higuchi model.

In conclusion, it is possible to reduce the burst effect from hydrophilic matrix extend release dosage forms with highly soluble drug (as metoprolol) if the drug is granulated with a high amount of Eudragit NE 40D and the obtained granules are incorporated in the matrix by tableting.

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